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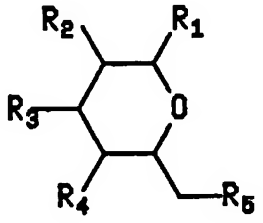
(57) Abstract

Compounds are provided which are crossreactive with peptides such as those which bind G-protein-linked receptors, together with preparative and therapeutic methods therefor. The compounds have general structure (3), wherein at least one of R_1, R_2, R_3, R_4 or R_5 comprises a functional group which is chemically similar to that found in the peptide of interest.



(3)

described. All of the G-protein-linked receptors analyzed to date contain from one to three potential sites of asparagine-linked glycosylation. The transmembrane signaling pathway used by G-protein-linked receptors represents one of the major mechanism of signal transduction in cellular systems. It is known, for example, that substance P acts as a vasodilator, a depressant, stimulates salivation, and produces increased capillary permeability. Substance P is a naturally occurring undecapeptide belonging to the tachykinin family of peptides, the latter being so-named because of their prompt contractile action on extravascular smooth muscle tissue. In addition to substance P (neurokinin-1, NK-1), the known mammalian tachykinins include neurokinin A (NK-2) and neurokinin B (NK-2). The tachykinins have been implicated in gastrointestinal (GI) disorders and diseases of the GI tract, such as inflammatory bowel disease, ulcerative colitis and Crohn's disease.

Substance P is known to produce both analgesia and hyperalgesia in animals, depending on dose and pain responsiveness of the animal and plays a role in sensory transmission and pain perception. Substance P also is believed to be involved in the inflammatory response in diseases such as rheumatoid arthritis and osteoarthritis. Other disease areas where the tachykinins are believed to be involved include allergic conditions, immunoregulation, bronchospasm, reflex or neuronal control of the viscera, and Alzheimer's disease and Downs Syndrome.

To date, there have been limited therapeutic applications involving peptides, due in considerable part to lack of oral bioavailability and to proteolytic degradation. Typically, for example, peptides are rapidly degraded *in vivo* by exo- and endopeptidases, resulting in generally very short biological half-lives. Another deficiency of peptides as potential therapeutic agents is their lack of bioavailability via oral administration. Degradation of the peptides by proteolytic enzymes in the gastrointestinal tract is likely an important contributing factor. The problem is, however,

more complicated, because it has been recognized that even small, cyclic peptides which are not subject to rapid metabolic inactivation nevertheless exhibit poor oral bioavailability. This likely is due to poor transport across the intestinal membrane and rapid clearance from the blood by hepatic extraction with subsequent excretion into the intestine. These observations suggest that multiple amide bonds may interfere with oral bioavailability.

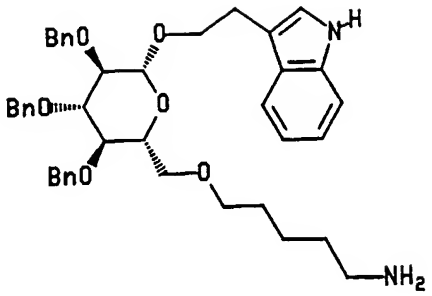
The design of peptide mimics which are resistant to degradation by proteolytic enzymes has become of increasing interest to peptide chemists, both for hormone agonist/antagonist and for enzyme inhibitor design. A primary goal has been to reduce the susceptibility of mimics to cleavage and inactivation by peptidases. In one approach, such as disclosed by Sherman and Spatola, *J. Am. Chem. Soc.*, *112*, **1990**, 433, one or more amide bonds have been replaced in an essentially isosteric manner by a variety of chemical functional groups. This stepwise approach has met with some success in that active analogs have been obtained. In some instances, these analogs have been shown to possess longer biological half-lives than their naturally-occurring counterparts. Nevertheless, this approach has limitations. Successful replacement of more than one amide bond has been rare. Consequently, the resulting analogs have remained susceptible to enzymatic inactivation elsewhere in the molecule. Moreover, this approach does not permit generalizations between chemically unrelated peptides concerning permissible amide mimic substitutions.

In another approach, a variety of uncoded or modified amino acids such as D-amino acids and N-methyl amino acids have been used to modify mammalian peptides. Alternatively, a presumed bioactive conformation has been stabilized by a covalent modification, such as cyclization or by incorporation of γ-lactam or other types of bridges. See, e.g., Veber and Hirschmann, *et al.*, *Proc. Natl. Acad. Sci. USA*, **1978** 75 2636 and Thorsett, *et al.*, *Biochem Biophys. Res. Comm.*, **1983** 111 166. The primary purpose of such

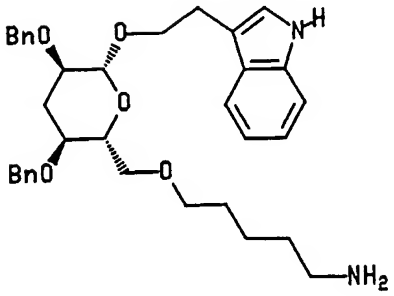
manipulations has not been to avoid metabolism or to enhance oral bioavailability but rather to constrain a bioactive conformation to enhance potency or to induce greater specificity for a receptor subtype.

Another approach, disclosed by Rich, D.H. in *Protease Inhibitors*, Barrett and Selveson, eds., Elsevier (1986), has been to design peptide mimics through the application of the transition state analog concept in enzyme inhibitor design. For example, it is known that the secondary alcohol of statine mimics the tetrahedral transition state of the scissile amide bond of the pepsin substrate. Again, increased potency rather than decreased susceptibility to peptidases or increased bioavailability was the principal objective. Moreover, the transition state analog concept has no apparent relevance to hormone agonist/antagonist design.

Nicolaou and Hirschmann, *et al.*, *Design and synthesis of a peptidomimetic employing β-D-glucose for scaffolding*, in Peptides, Rivier and Marshall, eds., ESCOM (1990), disclosed non-peptide somatostatin mimics having structures (1) and (2), wherein Bn is benzyl.



(1)



(2)

These mimics bound somatostatin receptors of AtT-20 cells with IC_{50} of about 9.5×10^{-6} M and about 1×10^{-6} M, respectively, compared with an IC_{50} of about 9.3 nM (9.3×10^{-9} M) for somatostatin itself. Significantly, the mimics failed to bind other G-protein-linked receptors at clinically acceptable concentrations. For example, while it was found that the β-adrenergic receptor, which is also found in AtT-20 cells, bound mimic (1), it required a five fold higher concentration to do so than was required for the somatostatin receptor. The goal of the authors was to increase the specificity of the mimics for the somatostatin receptor, not to develop compounds which would be bound by G-protein-linked receptors. Indeed, the authors suggested increasing the potency of the compounds as a means for enhancing this specificity.

Accordingly, there remains a long-felt need for metabolically stable chemical compounds which exhibit both good bioavailability and the capacity to bind a variety of G-protein-linked receptors.

OBJECTS OF THE INVENTION:

It is one object of the present invention to provide compositions of matter which mimic or inhibit the biological and/or chemical activity of peptides.

It is another object to provide compositions which are chemically more stable than naturally-occurring peptides, particularly under conditions such as found in the human body.

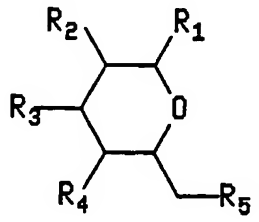
It is a further object to provide compositions which function as hormone agonists or hormone antagonists.

It is a further object to provide compositions which effectively bind G-protein-linked receptors, especially the substance P receptor.

It is still a further object to provide prophylactic, diagnostic, and therapeutic uses for peptide analogs.

SUMMARY OF THE INVENTION:

These and other objects are accomplished by the present invention, which provides compounds, known as peptide analogs, which contain no peptide bonds yet which mimic or inhibit the chemical and/or biological activity of peptides. In general, the peptide analogs of the invention have structure (3):



(3)

wherein at least one of R_1, R_2, R_3, R_4, or R_5 comprises a chemical functional group which causes the compounds to be crossreactive with the peptide of interest. In preferred embodiments, peptide analogs of the invention have the structure (4) and, more preferably, the structure (5):